## Remarks/Arguments

Claims 1-3 and 52-54 appear in this application for the Examiner's review and consideration. Applicants present the following remarks to address the concerns expressed in the final Office Action dated September 12, 2007.

Claims 52-54 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. In particular, the Office alleges that the phrases "a therapeutically effective amount" and "at least one pharmaceutically acceptable excipient" do not find written description support in the specification because Applicants did not indicate the page and line numbers on which these phrases can be found. Applicants respectfully traverse.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail so that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See, e.g., Vas-Cath, Inc.*, 935 F.2d at 1563. As long as a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if not every nuance of the claims is explicitly described in the specification, the written description requirement is met. *In re Alton*, 76 F.3d 1168, 37 U.S.P.Q.2d 1578 (Fed. Cir. 1996). "*Ipsis verbis* disclosure is not necessary to satisfy the written description requirement." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996).

Claims 52-54 recite, in part, pharmaceutical formulations that comprise a therapeutically effective amount of ondansetron hydrochloride dihydrate and at least one pharmaceutically acceptable excipient. These claims are supported by original claims 45-47, which recite pharmaceutical formulations comprising ondansetron hydrochloride dihydrate.

Although original claims 45-47 do not expressly recite "a therapeutically effective amount" of ondansetron hydrochloride dihydrate or the inclusion of "at least one pharmaceutically acceptable excipient," one of ordinary skill in the art would recognize that these components are inherent in a "pharmaceutical formulation" of ondansetron hydrochloride dihydrate in view of the knowledge in the art at the time the application was filed. For example, one of ordinary skill in the art at the time the application was filed would have been familiar with U.S. patent No. 4,695,578 ("'578 patent"), which discloses pharmaceutical compositions of a class of compounds that includes ondansetron. '578 patent, col. 4, ll. 44-51. The '578 patent states that the pharmaceutical compositions may be formulated "in conventional manner using one or more physiologically acceptable carriers or

excipients." *Id.* at col. 4, ll. 52-54. Thus, one of ordinary skill in the art would have recognized that a pharmaceutical formulation comprising ondansetron would include "at least one pharmaceutically acceptable excipient." In addition, the '578 patent states that a proposed dose of the ondansetron or other compound of the class is 0.5 to 20 mg of the compound per unit dose, but may vary depending on the age and weight of the patient as well as the severity of the condition to be treated. *Id.* at col. 5, l. 62 to col. 6, l. 7. Thus, one of ordinary skill in the art would have recognized that a pharmaceutical formulation comprising ondansetron would also include a therapeutically effective amount of ondansetron. *Ipsis verbis* disclosure is not necessary to satisfy the written description requirement.

For these reasons, claims 52-54 comply with the written description requirement of 35 U.S.C. § 112, first paragraph. According, the rejection of the claims on this ground cannot stand and should be withdrawn.

Claims 1-3 and 52-54 stand provisionally rejected on the ground of non-statutory obviousness-type double patenting over claims 26-29 of co-pending U.S. application Serial No. 11/482,486. Applicants wish to defer response to this rejection until the claims of this application or of co-pending U.S. application Serial No. 11/482,486 are in condition for allowance.

Claims 1-3 and 52-54 remain rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Zhongguo Yiyao Gongye Zazhi 24, 241-242 (1993) ("the Zhongguo reference"), U.S. patent Nos. 4,845,115 to Tyers *et al.*, ("'115 patent"), 4,695,578 to Coates *et al.*, ("'578 patent"), 4,835,173 to Tyers ("'173 patent"), and PCT publication WO 02/36558 ("the WO '558 publication") for the reasons set forth on pages 8-15 of the Office Action. Applicants respectfully traverse.

The U.S. Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 127 S. Ct. 1727, 1740-41 (2007) recently addressed the proper mechanics of an obviousness rejection, stating that in determining motivation to arrive at a claimed invention with a reasonable expectation of the success:

> [I]t will often be necessary to look to interrelated teachings of multiple patents; to the effect of demands known to the design community or present in the marketplace; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit.

The essence of the Office's rationale for rejecting the claims as obvious in view of the cited references is as follows:

> One of ordinary skill in the art would be motivated to prepare a purer form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g., improved solubility, shelf-life, improved mode of administering properties, etc.

Office Action, pp. 10-11.

In view of the U.S. Supreme Court's recent decision in *KSR*, as well as the decisions cited below, this argument alone is not legally sufficient to establish that the pure ondansetron hydrochloride dihydrate recited in the claims is *prima facie* obvious in view of the cited references.

In order to render a new form of a compound obvious, the prior art must do more than merely suggest its existence.

> [T]o have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

*Pfizer v. Apotex*, 480 F.3d 1348, 1365 (Fed. Cir. 2007).

Applying the *Pfizer* reasoning, the Federal Circuit and its predecessor Court of Customs and Patent Appeals have consistently held that in order for a claim to new form of a known compound to be *prima facie* obvious, the prior art must both provide some guidance as to the new form of the compound and provide some guidance as to a process for preparing the new form of the compound, such as discussed in *In re Hoeksema*, 399 F.2d 269 (C.C.P.A. 1968). *See* Amendment dated May 2, 2007, pp. 5-7 (citing *In re Hoeksema*; *In re Cofer*, 354 F.2d 664, 667-68 (C.C.P.A. 1966); and *In re Kumar*, 418 F.3d 1361 (Fed. Cir. 2005)).

The Federal Circuit again reiterated this position in the recent case of *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 2007 U.S. App. LEXIS 21753, Case No. 2006-1530, -1555 (Fed. Cir. 2007), concluding that "a purified compound is not always prima facie obvious over [a less pure form of the compound]; for example,...the state of the art may be such that discovering how to perform the purification is an invention of patentable weight in itself."

Claims 1-3 and 52-54 recite a new form of the known compound ondansetron hydrochloride dihydrate – "Ondansetron hydrochloride dihydrate having a purity of at least about 99.0% by weight and an exo-methylene by-product content of less than 0.01% by weight."

As previously argued, the cited art does not explicitly or inherently disclose or provide any guidance as to the purity of the compound recited in the claims. *See, e.g.*, Amendment dated August 14, 2006, pp. 7-8.

Further, as argued in detail in the Amendment dated May 2, 2007, none of the cited art, either alone or in combination, teaches or provides any guidance as to a suitable method for obtaining ondansetron hydrochloride dihydrate of the purity recited in the claims. *See* Amendment dated May 2, 2007, pp. 7-11.

Applicants have made ondansetron hydrochloride dihydrate having a purity of at least about 99.0% by weight and less than 0.01% by weight of exo-methylene by-product from ondansetron base using a two-prong approach: (i) minimizing the amount of exo-methylene by-product present in the starting ondansetron base by controlling the amount of methyl-imidazole starting material used to prepare the ondansetron base and (ii) purifying the ondansetron hydrochloride dihydrate by crystallization from water in the presence of activated carbon to reduce the exo-methylene by-product content to less than 0.01%. None of the cited art teaches or provides any guidance as to Applicants' two-prong approach, or any other method that can produce ondansetron hydrochloride dihydrate of the recited purity. *See* Amendment dated May 2, 2007, pp. 7-11.

In particular, the Rule 132 declaration of Dr. Lidor-Hadas ("the Lidor-Hadas declaration") provides evidence that the process disclosed in the Zhongguo reference at best can produce ondansetron hydrochloride dihydrate having an exo-methylene by-product content of 1.47%, which is at least 147-fold less pure than the ondansetron hydrochloride dihydrate recited in the claims. *See id.* at pp. 9-10. The Lidor-Hadas declaration also provides evidence that the process disclosed in the '578, '173, and '115 patents (collectively "the Glaxo patents") produces ondansetron hydrochloride dihydrate having an exo-methylene by-product content of 0.12%, which is at least 12-fold less pure than the ondansetron hydrochloride dihydrate recited in the claims. *See id.* at pp. 10-11. Finally, the WO '558 publication does not disclose any process for preparing ondansetron hydrochloride dihydrate at all, let alone ondansetron hydrochloride dihydrate having the recited purity. *See id.* at p. 11.

Thus, because the cited references, either alone or in combination, do not teach or provide any guidance as to ondansetron hydrochloride dihydrate of the recited purity or a suitable process for obtaining ondansetron hydrochloride dihydrate of the recited purity, the Office has not made out a *prima facie* case of obviousness.. *In re Hoeksema, supra.* Nevertheless, the Office improperly shifts the burden to Applicants to come forward with secondary evidence as to the properties of the claimed compounds, such as improved solubility, shelf-life, or improved administrability. Office Action, pp. 10-11. However, since the Office has not met its burden to establish a *prima facie* case of obviousness, it is improper to shift the burden to Applicants to come forward with such objective evidence.

For these reasons, the rejection of claims 1-3 and 52-54 under 35 U.S.C. § 103(a) as rendered obvious by the Zhongguo reference, the '115 patent, the '578 patent, the '173 patent, and the WO '558 publication cannot stand and should be withdrawn.

In view of the foregoing arguments, it is believed that claims 1-3 and 52-54 are in condition for allowance, early notice of which would be appreciated. If any outstanding issues remain, the Examiner is invited to telephone the undersigned at the telephone number indicated below to discuss the same. No fee is believed to be due for the submission of this response. Should any fees be required, please charge such fees to Kenyon & Kenyon, LLP Deposit Account No. 11-0600.

Respectfully submitted,

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